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INTERNATIONAL PATENT APPLICATION
UNDER THE PATENT COOPERATION TREATY (RO/US)

International Application No.	PCT/US00/16989	
Applicant:	The Wistar Institute of Anatomy and Biology	
Filed:	21 June 2000	
For:	NOVEL PYRRHOCORICIN-DERIVED PEPTIDES, AND METHODS OF USE THEREOF	July 13, 2001

Assistant Commissioner for Patents
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Washington, D.C. 20231

RESPONSE AND AMENDMENT UNDER RULE 66.3

Sir:

In timely response to a First Written Opinion dated 29 May 2001, kindly enter the following Response and substitute pages.

Presented herewith are substitute pages 42, 43, 48, 49 and 53 (replacing original pages 42, 43, 48, 49 and 53) containing Amended claims 1, 5, 41, and 47 and new claims 73-75.

A. Amended and New Claims

The claims have been amended as follows:

Claim 1 has been amended by inserting the phrases " wherein said Thr is not glycosylated" into the claim; and by inserting that R^1 is "other than L-Val". For support, see page 6, lines 7-11 and the modified peptides reported in pages 24-28.

Claim 5 has been amended by deleting the phrase "L-Val-" from the choice of R^1 group.

Claim 41 has been amended to clarify the various selections of the R^2 group by reciting that the additional amino acids may be naturally occurring or unnatural amino acids, and adding that the additional additional amino acids may link at least two peptides. This claim is supported at page 9, lines 12-13 and page 10, line 3 through page 12, line 6.

Claim 47 has been amended by replacing the term "comprises" with "is".

New Claim 73 recites a peptide of Amended Claim 1, which is fused to a second protein. This claim is supported in the original specification at page 10, lines 10-12.

New Claim 74 recites a composition according to claim 41, wherein R^2 of one said peptide is a β-acetyl-2,3- diamino propionic acid group and wherein an additional said peptide is linked to the same R^2 at the carboxyl terminus. This claim is supported at page 9, lines 12-13 and page 10, line 3 through page 12, line 6.

New Claim 75 repeats the language of original Claim 1 and inserts the phrase " wherein said Thr is not glycosylated" into the claim. Applicant notes that new claim 73 is added to retain the original disclosure of R^1 of SEQ ID NO: 1 for the purposes of further argument during national phase prosecution.

No new matter is added to this application by introduction of these amendments or new claims.

B. Rejection for Lack of Novelty

Claims 1-4 and 30 were found to lack novelty under PCT 33(2) as being anticipated over R. Hoffman *et al*, 1999 *Biochim. Biophys. Acta, 1426*:459-467 because Hoffman discloses a peptide which consists of the formula of SEQ ID NOS: 1 and 16.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reasons.

Amended Claim 1 discloses a SEQ ID NO: 1 of the present application which encompasses a peptide of the definition R^1-Asp-Lys-Gly-X-Y-Leu-Pro-Arg-Pro-Thr-Pro-Pro-Arg-Pro-Ile-Tyr-X'-Y'-R^2, wherein the Thr in the sequence is *not glycosylated* and R^1 is not L-Val. X and Y form a dipeptide Ser-Tyr or a dipeptide formed of naturally occurring amino acids or unnatural amino acids, the dipeptide

resistant to cleavage. X' and Y' form a dipeptide Asn-Arg, or a dipeptide formed of naturally occurring amino acids or unnatural amino acids, the dipeptide resistant to cleavage. SEQ ID NO: 16 is the peptide of SEQ ID NO: 1, wherein R^1 is D-Val and R^2 is D-Asn.

In contrast, Hoffman discloses three pyrrhocoricin sequences: native or synthetic Pyr G, a synthetic non-glycosylated peptide Pyr nG, and a glycosylated peptide Pyrrhocoricin 1-18nG. Pyr G (native or synthetic) has the sequence of the present SEQ ID NO: 1, where R^1 is L-Val, and R^2 is L-Asn, and the Thr in position 11 is glycosylated. Pyr nG has the sequence of SEQ ID NO: 1, where R^1 is L-Val, and R^2 is L-Asn-NH_2. Pyrrhocoricin 1-18nG differs from SEQ ID NO: 1 in that it does not contain the dipeptide X'Y' at the carboxyl terminus of SEQ ID NO: 1.

Hoffman's peptides do not anticipate the present claims 1-4 and 30. Amended Claim 1 defines a peptide of SEQ ID NO: 1, wherein the Thr residue is not glycosylated and R^1 is not L-Val. Thus, neither Hoffman's native or synthetic PyrG meets this peptide definition of Amended Claim 1, since the single Thr in native or synthetic PyrG described by Hoffman is glycosylated. Pyrrhocoricin 1-18nG differs from SEQ ID NO: 1 in that it does not contain the dipeptide X'Y' at the carboxyl terminus of SEQ ID NO: 1. Pyr nG cannot meet the definition of SEQ ID NO: 1 of Amended Claim 1, because its "R^1" position is L-Val.

Amended Claim 2 defines a peptide of SEQ ID NO: 1 with an R^1 group of an alkyl group (a), an alkanoyl group (b), a positively charged reporter group (c), or between 1-15 additional amino acids of L or D configuration (d), said amino acids (d) being optionally substituted with an alkyl group (a), an alkanoyl group (b), a positively charged reporter group (c), or being capable of cyclizing the peptide. None of the peptides described by Hoffman contains these specific N-terminal modifications. In fact all of Hoffman's peptides require the R^1 group to be L-Val, which was excluded by Amended Claim 1. L-Val is not an alkyl group, an alkanoyl group or a reporter group or a D configuration amino acid (substituted or unsubstituted) as defined by the specification. Since L-Val is excluded by Amended Claim 1, it is necessarily excluded in the language of this dependent claim. The specific modifications of Amended Claim 2 are not suggested by Hoffman. Thus, Hoffman's description of peptides cannot

anticipate the subject matter of Amended Claim 2. Amended Claim 2 should be properly free of this rejection.

Claim 3 defines a peptide of SEQ ID NO: 1 with an R^1 group of between 1 to 15 additional amino acids, which have been cyclized by the insertion into the structure of the amino acid of a modifying sugar or imide. None of the peptides described by Hoffman contains that specific N-terminal modification. Nor is that specific modification suggested by Hoffman. Thus, Hoffman's description of peptides cannot anticipate the subject matter of claim 3. Claim 3 should be properly free of this rejection.

With regard to claim 4, which requires the R^1 group of SEQ ID NO: 1 to be 1-aminocyclo-hexane carboxylic acid, none of the peptides described by Hoffman contains that specific N-terminal modification. Nor is that specific modification suggested by Hoffman. Thus, Hoffman's description of peptides cannot anticipate the subject matter of claim 4. Claim 4 should be properly free of this rejection.

With regard to claim 30, SEQ ID NO: 16, none of the peptides described by Hoffman contain the unnatural D-form of the N-terminal Val or C-terminal Asn of SEQ ID NO: 16. In fact, Hoffman does not even suggest a modification of his peptides by use of the alternative D form of amino acids. Thus, nothing in Hoffman anticipates SEQ ID NO: 16 or claim 30. Claim 30 should therefore be free of this rejection.

The Pyrrhocoricin 1-18nG does not have the identical amino acid sequence of SEQ ID NO: 1 because the amino acid Y' is missing. This peptide therefore cannot be used to anticipate SEQ ID NO: 1 or 16 or any of claims 1-4 or 30, since all of these claims require the Y' amino acid. In fact this amino acid cannot be omitted from the claimed peptides because it is necessary to form a cleavage-resistant dipeptide with the X' amino acid.

No other peptide described in Hoffman meets the requirements of SEQ ID NO: 1 and SEQ ID NO: 16 of Amended Claim 1, nor original claims 2-4 and 30.

In view of the above claim amendments and these remarks, Claims 1-4 and 30 are free of the above-noted novelty rejection.

C. Rejection for Lack of Inventive Step

Claims 1-4 and 30 were found to lack inventive step under PCT 33(3) and inventive step under PCT 33(3) over R. Hoffman *et al*, 1999 *Biochim. Biophys. Acta, 1426*:459-467 because the reference allegedly anticipates the claim invention.

In view of the above-amendment to Claim 1 and the remarks above, Applicant respectfully requests reconsideration and withdrawal of this rejection. The novelty rejection against claims 1-4 and 30 are rebutted by amendment and the remarks which distinguish Hoffman's disclosures from the invention. Further, Hoffman fails to suggest the additional modifications to the peptides encompassed by Amended Claim 1 and original claims 2-4 and 30. Therefore, Applicant submits that Amended Claim 1, and original claims 2-4 and 30 are free of this rejection.

Applicant acknowledges with appreciation the examiner's indication that claims 5-29 and 31-72 meet the criteria set out in PCT Article 33(2)-(4). New Claims 73 and 74 are believed to meet the same criteria. In view of these amendments and remarks, Applicant respectfully urges the examiner to find pending claims 1-74 to meet all requirements of PCT Articles 33(2)-(4).

The Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account Number 08-3040.

Respectfully submitted,

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